



Mycology Class 2

Fungal physiology,
immune response,
antifungal



Contact information

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OBJECTIVES

- ☐ Characteristics of fungi relevant to medicine
- ☐ Immune response against fungal infection
- ☐ Mechanism of action of antifungal drugs
 - Treatment of mycotic diseases



Activities of fungi - special relevance to medicine

- 1. Extracellular enzymes/components**
- 2. Polyol production**
- 3. Metabolites**
- 4. Trace elements**

Extracellular enzymes/components

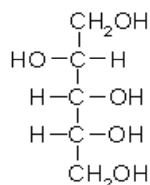
- **Degrade polymers for cell nutrition**
 - Carbohydrates: mono- and disaccharides
 - Proteins: di- and tri-peptides
- **Associated with wall and released from cell**
- **Virulence factors**
 - e.g.; keratinase attack skin protein -> Dermatophytes.
 - Collagenases: Zygomycetes (rhinocerebral zygomycosis).
- **Antigenic**
- **Modify the wall to allow branching: spore release**
- **Interact with defense in macrophages (evasive mechanisms):**



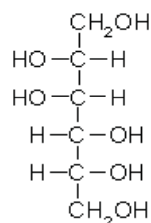
Polyol production:

- **Nutrient sources**
- **Free radical scavengers may help protect against phagocytic killing**
- **D-mannitol and D-arabinitol are produced by several fungi.**

D-arabinitol



D-Mannitol





Diagnostic value:

1. D-arabinitol (yeast)

Produced during invasion by many *Candida* species:

C. albicans

C. tropicalis

C. parapsilosis

Cleared by kidneys in same manner as creatinine. Elevated arabinitol:creatinine ratio associated with invasive disease since arabinitol is higher than expected level

2. D-mannitol (filamentous fungi)

Aspergillosis

Cryptococcosis



Metabolites

Many metabolites excreted in varying amounts depending of the nutrient balance: not necessarily during human infection.

Many industrial uses

penicillin

cyclosporin A

ethanol

oxalic acid

citric acid



Trace elements

Iron (Fe)

- Battle for iron between host transferrin/ lactoferrin and the fungus.
 - Some fungi produce iron chelators that transport Fe into cells.
- Ringworm species (dermatophytes) unable to compete – may explain why restricted to dead cell layers of skin, and hair and nail.
- *Histoplasma capsulatum* and *Penicillium Marneffeii*-> intracellular pathogens.
 - Glutathione-dependent extracellular ferric reductase
- Zygomycosis and iron chelator (deferoxamine) to treat hemochromatosis.



Immune response against fungal infection

■ Ag. variation during development of the infection.

Aspergillus

Conidia spores (shedding, swelling and new antigens are expressed)



Hyphal filaments
(more antigens exposed)

Candida

Yeast, pseudohyphae, hyphae

Switching of surface antigens *in vivo*.



Distinct host humoral and cellular responses

Status of the host

- Normal individuals-> Asymptomatic infection or self-limited.
 - Immuno-compromised individuals
 - ☐ AIDS
 - ☐ Diabetes
 - ☐ Corticoids treatments, etc
- } OPPORTUNITICS Fungi

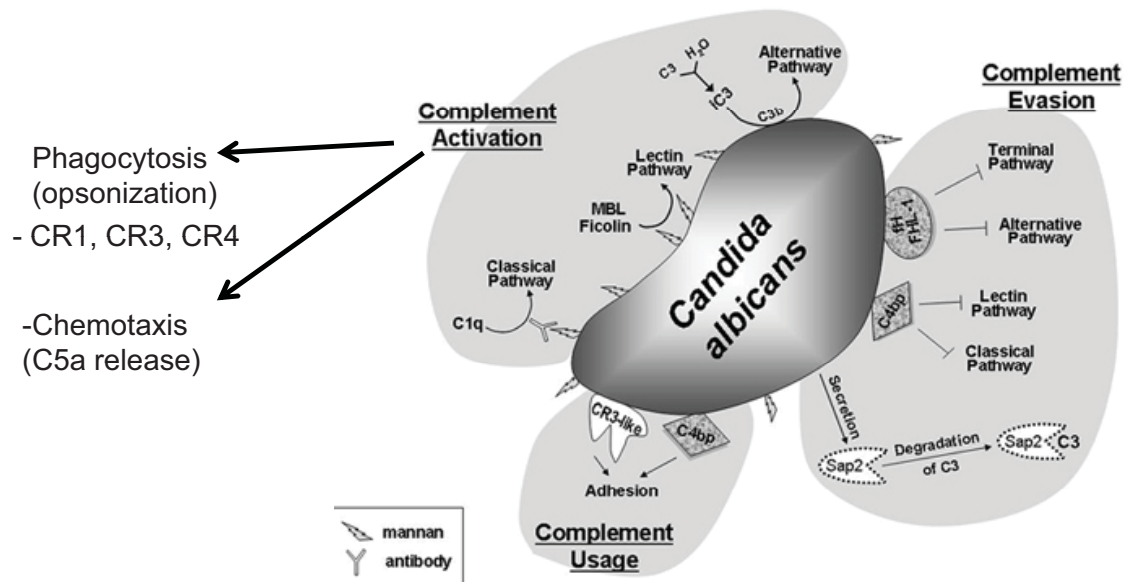
Non-immune factors in host defenses.

- Skin, mucous membrane, competition for nutrients, mucocilliary clearance system of the respiratory tract.
 - Burning, surgical wound
 - Intravenous catheters
 - Antibiotics treatment
 - Iron chelators treatment (**Deferoxamine**)
 - Hemochromatosis: genetic or acquired - > Zygomycosis.

Host vs pathogen

- “Extreme immune response”
 - Mediastinal fibrosis -> Histoplasmosis
- Poor immune response
 - AIDS => High # Cryptococcosis (“no inflammatory responses”)
 - Treatment with antiviral drugs-> life-threatening immune response inflammatory syndrome.
- Immune-mediated hypersensitivity reactions.
 - Asthma, allergic bronchopulmonary aspergillosis.

Innate immune system- Complement system



Front Biosci (Elite Ed). 2009 Jun 1;1:1-12

Innate immune system-

- Pentraxins (PTX3). Pattern recognition molecules-> impair phagocytosis (Aspergillosis)
- Anticandidal peptides (β -defensin, Histatin) -> predisposition of patient with xerostomia (dry mouth) to oral candidiasis

Neutrophils

- Phagocytosis of opsonized or non opsonized fungi.
 - Opsonized: Antibody or complement
 - Non opsonized: mannose and β -glucan residues found in the pathogens are recognized by PMN
- Release of complement components, chemokine (IL-8)
- Oxidative stress: H_2O_2 and Hypochlorous acid
 - PMN kills hyphal structures
- Microbial activity ; defensins, lactoferrin.



Phagocytosis

Neutropenia

- *Candida* spp (disseminated disease)
- *Aspergillus* spp (52% neutropenia)
- Zygomycosis (20%)
- *Fusarium* spp
- *Trichosporon* spp
- Chronic granulomatous disease (CGD); failure of NADPH oxidase-> susceptible to:
 - Catalase (+) bacteria (*S. aureus*)
 - *Aspergillus* spp
 - *Candida* spp

Mononuclear cells

- Macrophage.

- ☐ Kills efficiently conidia but not hyphal structures.
- ☐ *H capsulatum* can survive inside macrophages.

Acquired immune system- Antibody

Remain controversial

- B-deficiency (animal model)-> no effect on infection with *Candida*, *H. capsulatum*.
- Humoral immunity -> disseminated candidiasis
 - ☐ Specific immune response against certain Ags.
 - ☐ Cryptococcosis in patients with Hypogammaglobulinemia
- Pathogenesis of allergic responses to inhaled fungi. IgE and IgG specific to fungal Ags -> pathogenesis of chronic rhinosinusitis.

Acquired immune system- T cells

□ **CD4**; CD8

□ **CD4 T helpers**

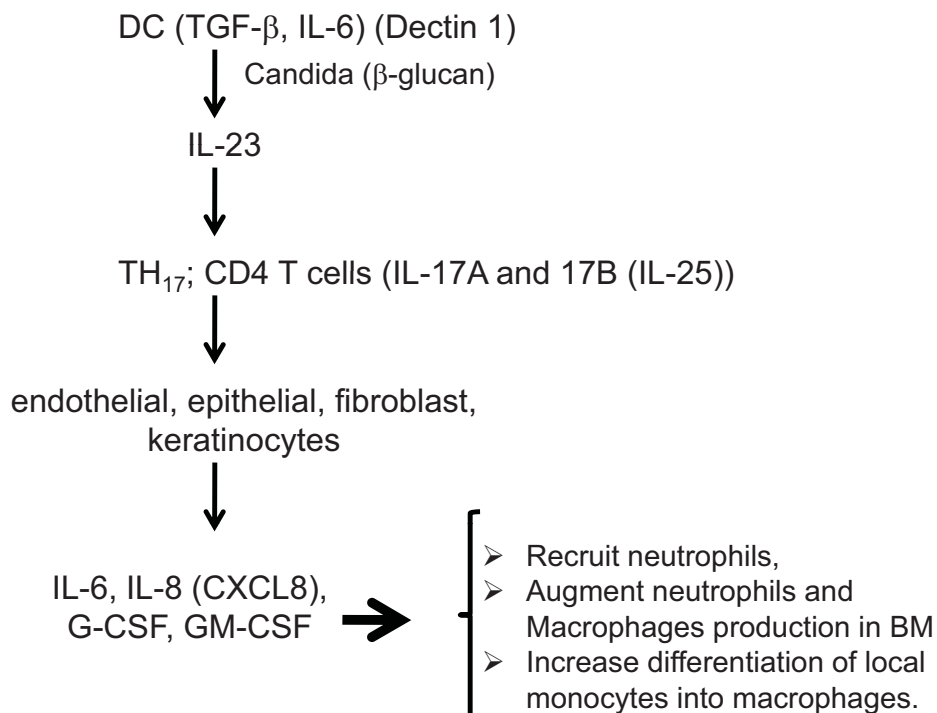
■ **TH₁** and **TH₁₇**

- Conidia and yeast->**TH₁**. *Candida* spp, *A. fumigatus* (conidia), dimorphic fungi
- *Candida* spp, *Aspergillus* -> **TH₁₇**
- TH₂ -> Hyphal forms

□ **Disease**

- *C. neoformans*, *P.jiroveci*, and dimorphic infection.
- *Candida* infection (mucosal infection)-> HIV

Link: CD4 and neutrophil and macrophage

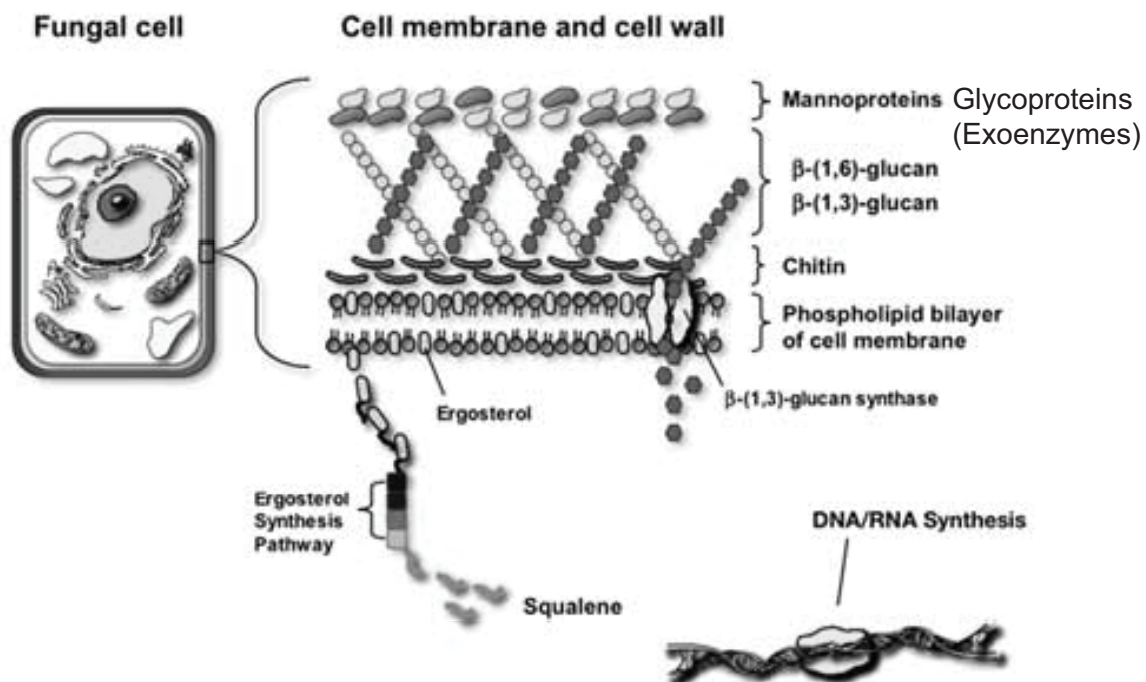


Predisposing factor	Etiologic agents(s)
Traumatized skin and mucosa surfaces	<i>Candida</i> spp
Neutropenia	Candida spp (disseminated disease)
	<i>Aspergillus</i> spp
	Zygomycosis agents
	<i>Fusarium</i> spp
	<i>Trichosporon</i> spp
Impaired T cell-mediated immunity	Candida spp (mucocutaneous disease)
	<i>Cryptococcus neoformans</i>
	<i>Histoplasma capsulatum</i>
	<i>Coccidioides immitis</i>
	<i>Pneumocystis jiroveci</i>
	<i>Paracoccidioides brasiliensis</i>
	<i>Penicillium marneffe</i>
Chronic granulomatous disease	<i>Aspergillus</i> spp
	Candida <i>albicans</i> (disseminated disease)
Diabetes mellitus/Ketoacidosis	Agents of zygomycosis
Deferoxamine therapy	Agents of zygomycosis
Graft-versus-host disease	<i>Aspergillus</i> spp



Antifungal agents

Cell membrane and cell wall





Best target is only in fungi not in humans.

■ **Fungitoxic drugs:**

- ☐ Cause fungal death

■ **Fungistatic drugs:**

- ☐ Prevent further growth (gives immune system time to catch up)



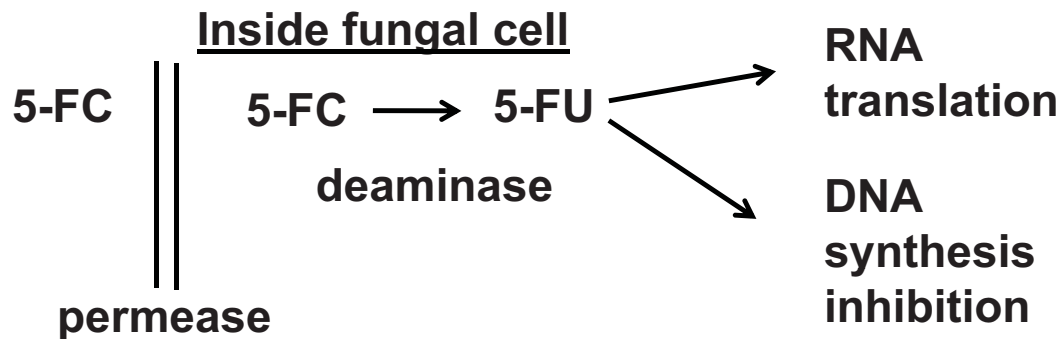
PRIMARY ANTI-FUNGAL AGENTS

1. 5-fluorocytosine (5-FC)
2. Polyenes
3. Azoles
4. Griseofulvin
5. Allylamines
6. Echinocandins
7. Whitfield ointment
8. Trimethoprim –sulfamethoxazole (*).

*Used mainly in infections caused by bacteria,
but also for fungal infection caused by *Pneumocystis jiroveci* (HIV + individuals)

5-fluorocytosine (5-FC)

- **Fungicidal (Candida and Cryptococcus)**
 - Enters via cytosine permease
 - Deaminated to 5-fluorouracil (5-FU) (cytosine deaminase absent in human cells)
- **Bone marrow suppression and alopecia**
- **Resistance often seen when not used in combination with other antifungal drugs (Candida)**
 - Permease reduction
 - Deaminase reduction



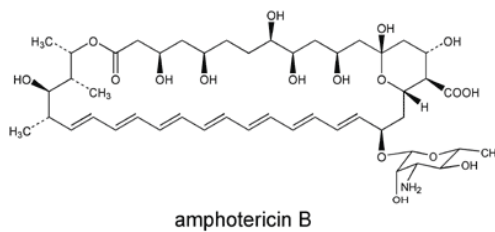
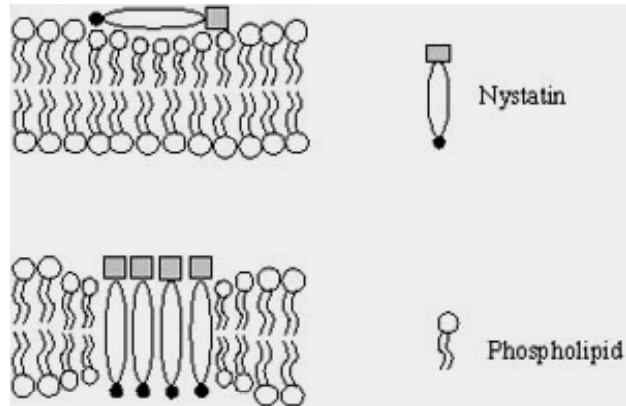
Polyenes (Fungal sterols)

- **Bind to ergosterol and form ion channels in fungal membrane**
- **The permeability of the fungal cell wall is altered and the intracellular contents leak (potassium leak)**
 - **Ergosterol: C28 sterols (Humans cells have C27 sterols i.e.; cholesterol)**
- **First fungitoxic drugs (candida)**
 - **Nystatin**
 - Mucosal infection (topical) and oral to decrease intestinal levels of Candida (not absorbed)
 - **Amphotericin B deoxycholate: (Broad spectrum; amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-amphotericin B))**
 - intravenously or intraperitoneally (systemic candidiasis)
 - fever, chills, and myalgia
 - **Nephrotoxic:** azotemia, decreased glomerular filtration, loss of urinary concentrating ability, renal loss of sodium and potassium, and renal tubular acidosis (reduced nephrotoxicity if given as lipid complex or in liposomes)
- **Resistance is uncommon but when present usually is associated with reduced sterol in the cell membranes**

Fungal sterols

Ergosterol: C28 sterols
(Humans cells have C27 sterols i.e.; cholesterol)

Target for polyene antifungals (nystatin, amphotericin B)



Effect	Mechanism	Antifungals Involved	Suggested clinical management
Increased accumulation of renally-cleared drugs and/or drug vehicles Flucytosine, Fluconazole, Beta-lactams and many others...	Decrease in glomerular filtration	Amphotericin B	Consult package insert. Most drug dosages can be adjusted based on estimates of glomerular filtration (i.e. creatinine clearance). Use of a lipid amphotericin B formulation may help stabilize or slow declines in renal function.
Enhanced nephrotoxicity Aminoglycosides Cyclosporine Intravenous Contrast Dye Foscarnet and others...	Enhanced glomerular and tubular toxicity in the kidney	Amphotericin B	Minimize co-administration of nephrotoxic agents whenever possible. Consider first-line use of lipid amphotericin B formulation (L-amphotericin B) .

AMPHOTERICIN B

Disadvantages

- Intravenous administration
- Thrombophlebitis
- Nephrotoxic (Blood Urea Nitrogen (BUN), Creatinine)
- Fever
- Chills
- Anemia
- Long term administration

Ergosterol synthesis

Polyenes
(Nystatin and amphotericin B)

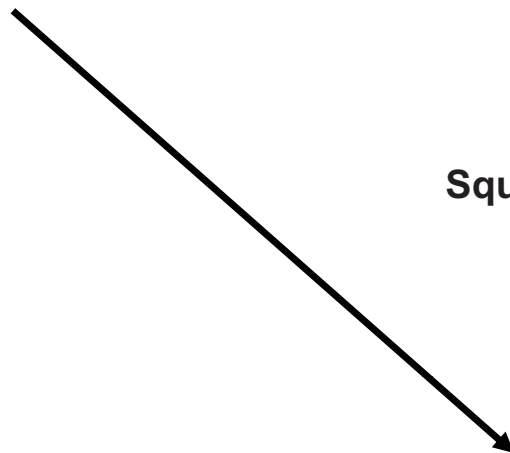
Acetyl CoA

Squalene

Squalene epoxide

Lanosterol

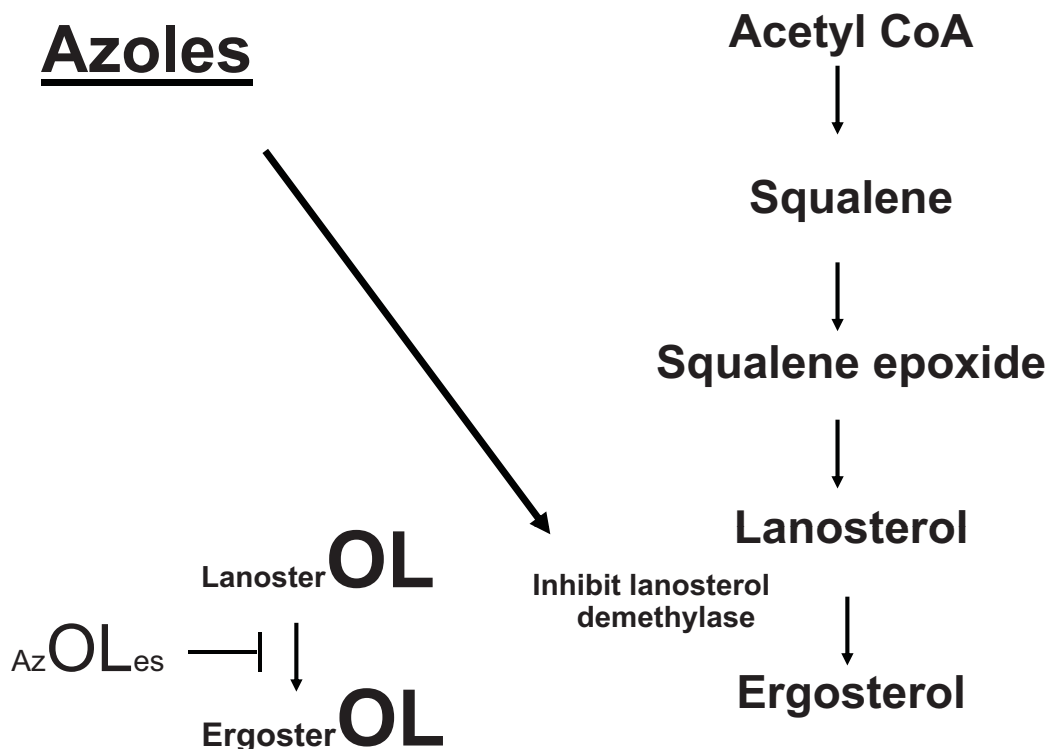
Ergosterol



Azoles (Candida spp, Cryptococcus neoformans)

- **Inhibit lanosterol demethylase**
 - Inhibit Ergosterol synthesis
- **Fungistatic (Wide and Broad; Dermatophytes, Systemic fungi, Candidiasis)**
 - Miconazole, Ketoconazole, Fluconazole, Itraconazole*, Voriconazole*, Posaconazole* ((*) Aspergillus, blastomycosis and histoplasmosis)
 - Oral absorption and solubility is optimal at acidic gastric pH (Ketoconazole)
 - Azoles, specially Ketoconazole, may have antiandrogenic effect, adrenal supression and liver dysfunction.
 - Teratogenic drugs (avoid pregnant women).
- **Azole resistance in *Candida albicans***
 - Several different types of resistance
 - Mutation in lanosterol demethylase
 - Upregulation of pumps exporting drug
 - ABC transporter
 - MDR (multiple drug resistance) type
 - In 1996, 10% cases of oral candidiasis in San Francisco were untreatable with fluconazole.
 - Mutations in *C. albicans* over 2 years: AIDS. fluconazole resistance
- **Different yeast species that are inherently resistant to azoles are appearing as important pathogens**

Azoles



Consideration of therapy

Effect	Mechanism	Antifungals Involved	Suggested clinical management
Decreased serum concentration of azole Antacids H ₂ Receptor antagonism Proton Pump Inhibitors Sulcralfate Didanosine (oral)	Decreased dissolution/absorption of solid dosage form	Ketoconazole, itraconazole (capsules),	Use solution formulation of itraconazole or other azole if indicated (i.e. voriconazole) Avoid taking antacids within 2 hours of oral azole therapy
Increased metabolism of azole Isoniazid, Rifampin, Phenytoin Carbamazepine Phenobarbital Ritonavir (voriconazole)	Induction of mammalian cytochrome-P450 mediated metabolism of azole	Ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole	Avoid concomitant use of these agents if possible. May require switch to <u>amphotericin B formulation or echinocandin</u>

Effect	Mechanism	Antifungals Involved	Suggested clinical management
Increased serum concentration of co-administered drug or metabolite Oral hypoglycemics, S-warfarin R-Warfarin Cyclosporin, Tacrolimus Phenytoin, Protease inhibitors (saquinavir, ritonavir) Busulfan Diltiazem Lovastatin Isoniazid, Rifampin, Rifabutin, Quinidine, etc.	Inhibition of cytochrome P450, P-gp, or both	Ketoconazole, itraconazole, voriconazole > fluconazole (usual doses)	Avoid concomitant use if possible. Severity of possible interaction is drug-dependent. Consult prescribing information of each drug to address interaction severity

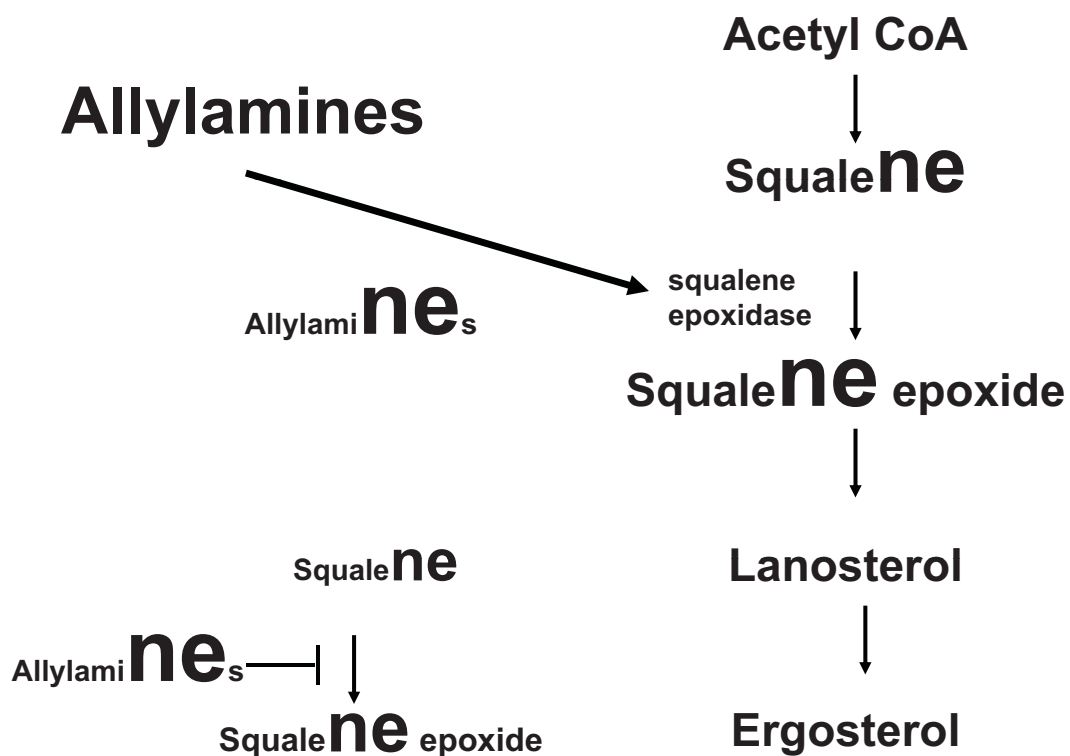
Allylamines

- Fungistatic/toxic

- Terbinafine = Lamisil®, naftidine

- Inhibit squalene epoxidase

- Accumulate in stratum corneum. High activity for ringworm infections





Echinocandins

- Caspofungin, micafungin
- **Inhibit $\beta(1-3)$ glucan synthetase** involved in forming carbohydrate polymers in hyphal walls.
- Approved for invasive **aspergillosis** and invasive and serious **mucosal candidiasis**
- Resistance when occurs has been linked to mutations in β -glucan synthase
 - Metabolism is cytochrome P450-independent

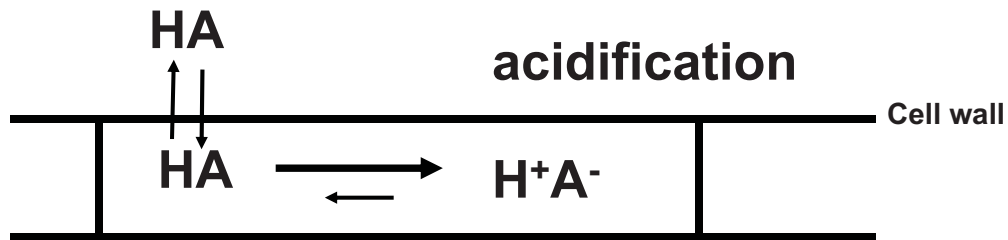


Griseofulvin

- Accumulates in **stratum corneum**
- Oral administration
- First effective oral therapy for **dermatophytes** (only fungi responding)
 - A slow acting drug used for skin and nail infections. It accumulates in the stratum corneum and prevent hyphal penetration through these layers
- Interferes with **microtubules and spindle** formation during mitosis
- **Disadvantages:** Photosensitivity, mental confusion, bone marrow suppression, and induces P-450

Whitfield ointment

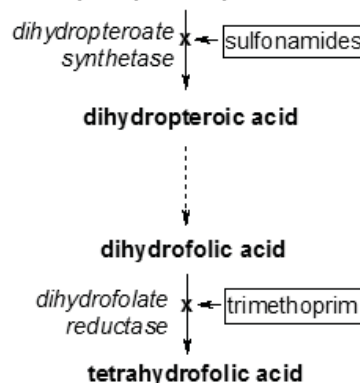
- May be caustic and impossible to use as systemic therapy
 - E.g. Salicylic acid, benzoic acid (weak acids, not ionized at lower pH)



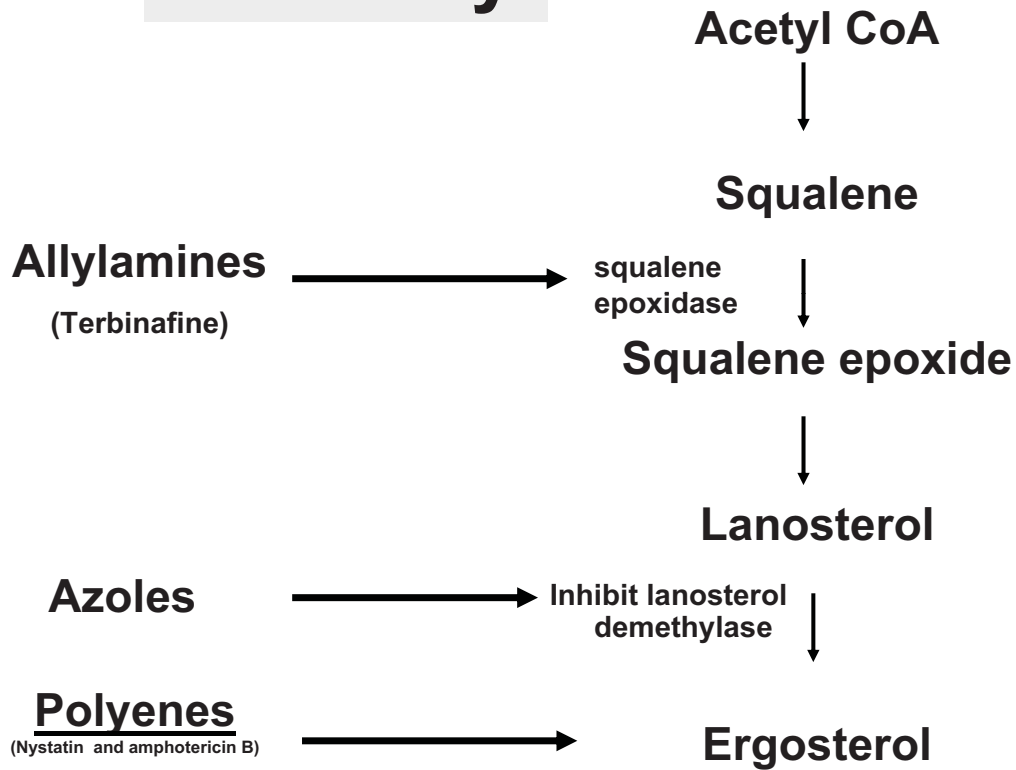
Trimethoprim - sulfamethoxazole

- Interfering with the action of bacterial dihydrofolate reductase.
 - Inhibit synthesis of tetrahydrofolic.
 - Affect precursor of the intermediate Thymidine monophosphate (dTMP)
 -> precursor of DNA metabolite (TTP).
- Use of trimethoprim is contraindicated during pregnancy
- Pneumocystis (*Pneumocystis jiroveci*) (AIDS). Also as prophylactic drug.

dihydropteroate diphosphate + p-aminobenzoic acid (PABA)



Summary



Summary

5-fluorocytosine

Inhibit RNA translation and DNA synthesis

Griseofulvin

Interferes with microtubules and spindle formation during mitosis

Echinocandins

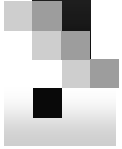
(Caspofungin, micafungin)

Inhibit $\beta(1-3)$ glucan synthetase; inhibit carbohydrate polymers in hyphal walls.

Drug	Mechanism of action	Treatment
Fluorocytosine (5-FC)	Inhibit RNA and DNA synthesis	Candida and Cryptococcus
Polyenes	Binds polyenes; alter membrane permeability	
- Nystatin		Mucosal (oral/intestinal) infection: candida
- Amphotericin B		Broad spectrum: systemic infection; penicilliosis
Azoles	Inhibit lanosterol demethylase	Broad spectrum: systemic infection
- Fluconazole		Dermatophytes, Candida (exception: <i>C. krusei</i> , <i>glabrata</i> , <i>guilliermondii</i>); <i>C. neoformans</i> , <i>C. immitis</i> .
- Itraconazole		Dermatophytes, Candida and <i>C. neoformans</i> (IV no accessible in US; no for systemic candidiasis); dimorphic fungi ; <u>Aspergillus</u> ; Phaeohyphomycetes
- Voriconazole		Dermatophytes, Candida and <i>C. neoformans</i> ; dimorphic fungi; <u>aspergillus</u> ; phaeohyphomycetes
- Posaconazole		Dermatophytes, Candida and <i>C. neoformans</i> ; dimorphic fungi; <u>aspergillus</u> ; phaeohyphomycetes
Griseofulvin	Interferes with microtubules and spindle	Dermatophytes
Allylamines	Inhibit squalene epoxidase	Dermatophytes
- Terbinafine		Dermatophytes
Echinocandins	Inhibit b(1-3) glucan synthetase	Candida and Aspergillus
(Caspofungin, micafungin, anidulafungin)		
Trimethoprim –sulfamethoxazole	Inhibit synthesis of tetrahydrofolic	Pneumocystis jirovecii; also prophylactic

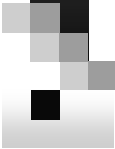
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Supplemental information

Classes 1 and 2



Overview of medically important fungi

Group (criteria based on Morphology and disease)				Diagnostic in vivo		Diagnostic in vitro		Natural habitat
	Disease	Etiologic agent form						
1. Molds Black fungi	Chromoblastomycosis	<i>Cladosporium carrionii</i>	Chestnut brown thick-walled Uniform cells 10 um in diameter	Branching chains of single-celled conidia	Woody plant material			
		<i>Fonsecaea pedrosoi</i>	Same			Series of single-celled conidia giving rise to series of secondary conidia	Same	
	Phaeohyphomycosis	<i>Exophiala jeanselmei</i>	Hyaline to brown yeast-like cells, filaments, septate hyphae, in various combinations	Single-celled conidia in balls at the apices of annellides	Woody plant material			
<i>Wangiella dermatitidis</i>		Same	Single-celled conidia in balls a thite apices of phialides and annellides			Soil and similar ambients		
		<i>Xylohypha bantiana</i>	Brown septate Hypahe	Sparsely branched, long chains of single-celled conidia				

Overview of medically important fungi (cont.)

Group (criteria

based on

Morphology and

disease

Diagnostic in vivo

form

Diagnostic in vitro

form

Natural habitat

3. Dimorphic	Blastomycosis	<i>Blastomyces dermatitidis</i>	Round to oval yeast s 8-15 um in diameter having broad-based budded daughter cells	Small, round, smooth single-celled conidia	Woody plants material
	Coccidioidomycosis	<i>Coccidioides immitis</i>	Spherules 30-60 um containing single-celled endospores 2-5 um in diameter	Alternating barrel shaped arthroconidia 2.5 - 4 by 3-6 um	Soil
	Histoplasmosis	<i>Histoplasma capsulatum</i>	Oval, intracellular yeasts 2-5 - 3.5 um in diameter	Tuberculate macrophages	Soil enriched by bat, starling or chicken droppings
	Paracoccidioidomycosis	<i>Paracoccidioides brasiliensis</i>	Multiple budding yeast, round budded cells 2-10 um attached to mature cells 30-60 um in diameter	Typically sterile	Probably woody plants
	Sporotrichosis	<i>Sporothrix schenckii</i>	Round to oval yeast 3-5 um in diameter	Conidia developing from sympodial conidiophores and from the hyphae	Woody plant material
4 Opportunistic infections	Aspergillosis	<i>Aspergillus fumigatus</i>	Septate, dichotomously branched hyphae 2.5 - 3.5 um in diameter	Chain of conidia from phialides Same	Same
		<i>Aspergillus fumigatus</i>	Same	Usually sterile, some isolate from phialides	
	Mycetoma	<i>Madurella mycetomatis</i>	granules in tissue and draining sinuses		

Overview of medically important fungi (cont.)

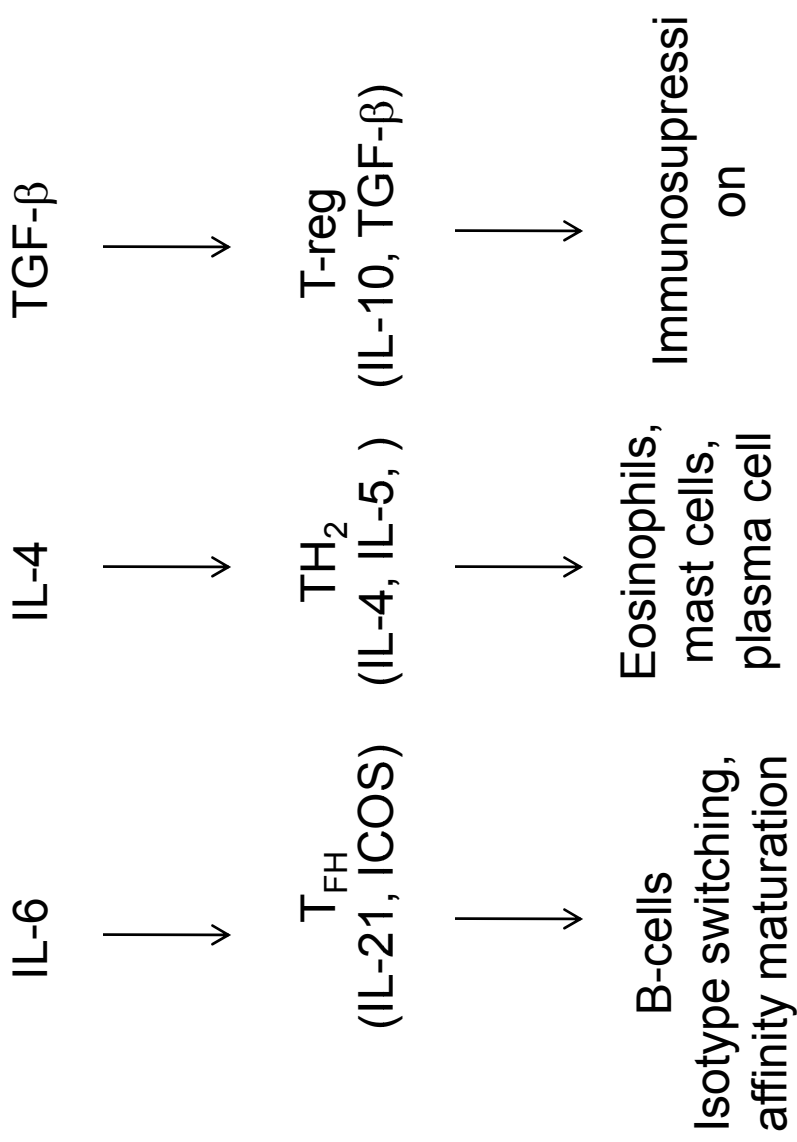
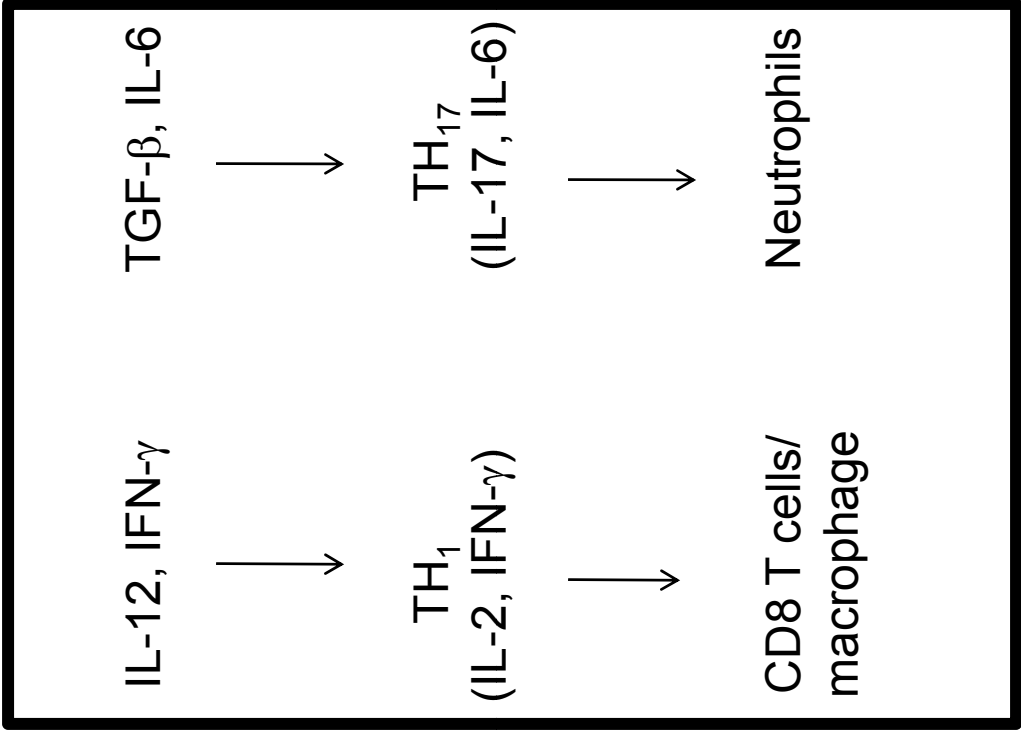
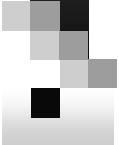
Group (criteria based on Morphology and disease)		Diagnostic in vivo				Diagnostic in vitro		Natural habitat
Disease	Etiologic agent form	Hyphae in scaly erythematous lesions, arthroconidia within and around hair (ectothrix)		Macro- and micro-conidia	Animals (zoophilic) Kittens/dogs			
2. Dermatophytes	Tinea capitis	<i>Microsporum canis</i>						
		<i>Trichophyton tonsurans</i>	Hyphae in scaly erythematous lesions, arthroconidia within hair (endothrix)	Conidia of various sizes and shapes			Human (anthropophilic)	
	Tinea corporis	<i>Microsporum gypseum</i>	Hyphae in stratum corneum	Macro- and micro-conidia			Soil (geophilic)	
		<i>Trichophyton mentagrophytes</i>	Same	Same			Humans and other animals (rodent, rabbits, etc)	
		<i>Trichophyton rubrum</i>	Same	Same			Humans	
	Tinea cruri/pedis	<i>Epidermophyton floccosum</i>	Hyphae in stratum corneum	Club-shaped conidia			Humans	
	Tinea cruri/pedis/ungium	<i>Trichophyton interdigitale (mentagrophytes)</i>	Same	Macro- and micro-conidia			Humans and other animals	
	Tinea cruri/pedis/ungium	<i>Trichophyton rubrum</i>	Same	Same			Humans	

Cell wall composition and taxonomic classification of representative medically important fungi

Principal cell wall polymer	Taxonomic Group	Examples
Chitin-chitosan	Zygomycetes	<i>Rhizopus arrhizus</i>
Chitin-glucan	Ascomycetes (mycelial)	<i>Pseudallescheria boydii</i>
	Basidiomycetes (mycelial)	<i>Schizophyllum commune</i>
Glucanmannan	Ascomycetes (yeast)	<i>Saccharomyces cerevisiae</i>
Chitin-mannan	Fungi imperfecti	<i>Candida albicans</i>
	Basidiomycetes (yeast)	<i>Filobasidiella neoformans</i>

	Hair Perforation Test	Urease Test	Growth at 37°C	Macro-conidia	Micro-conidia	Distinguishing Characteristics
<i>Trichophyton rubrum</i>	Negative	Negative	Positive	Pencil shaped/cigar shaped	Club shaped to pyriform, along the sides of the hyphae	Red reverse pigment Hair perf. test neg. Club shaped microconidia
<i>Trichophyton mentagrophytes</i>	Positive	Positive	Positive	Club shaped when present	Numerous Unicellular to round in grape like clusters	Round microconidia in grape like clusters Spiral hyphae
<i>Trichophyton tonsurans</i>	Usually (-) Occasionally +	Positive	Positive	Cylindrical to cigar shaped and sinuous, if present	Numerous, varying in shape and size, club shaped to balloon shaped	Microconidia varying in shape and size Growth enhanced by thiamine
<i>Trichophyton verrucosum</i>	Negative	Negative	Positive	“Rat-tailed” if present	Rare or Absent Chlamydospores in chains typically seen	Chlamydospores in chains Growth better on media with thiamine and inositol
<i>Trichophyton terrestre</i>	Positive	Positive	Negative	2-8 celled borne at right angles to hyphae	Club shaped with squared-off base on pedicels	Microconidia with squared-off base on short pedicels
<i>Epidermophyton floccosum</i>	Negative	Positive	Positive	Club shaped, often in clusters	Absent	Khaki colored colony with brown reverse Microconidia absent
<i>Microsporum canis</i>	Positive	Positive	NA	Fusoid, thick, rough walled with recurved apex	Typically absent Club shaped if present	Fusoid, rough walled macroconidia with recurved apex
<i>Microsporum gypsum</i>	Positive	Positive	NA	Ellipsoidal to fusiform, thin, Rough walled	Moderately abundant Club shaped	Thin walled macroconidia Tawny-buff granular colony
<i>Microsporum nanum</i>	Positive	Positive	NA	Typically 2 celled Pear or egg shaped Rough walled	Clavate when present	2 celled pear shaped macroconidia

Pathogen	Fungal ligand(s)	Phagocytic receptor(s)
<i>Aspergillus fumigatus</i>	Mannans, B-glucans	DC-SIGN, dectin-1
<i>Blastomyces dermatitidis</i>	BAD1	CR3, CD14
<i>Candida albicans</i>	Mannans, B-glucans	DC-SIGN, dectin-1
<i>Coccidioides posadasii</i>	Mannans, B-glucans	DC-SIGN, dectin-1
<i>Cryptococcus neoformans</i>	Glucoronoxylomannan	TLR2, TLR4, CD14, CD18, FcγRII
<i>Histoplasma capsulatum</i>	HSP60	CD18, VLA-5
<i>Pneumocystis jiroveci</i>	Mannans, B-glucans	DC-SIGN, dectin-1



Chemical Class Generic Name	Formulations	Indications
<u>Polyenes</u>		
Amphotericin B	C, L, O	CC
Nystatin	C, O, OS, P, VT, T	CC, OC, VC
<u>Azoles (Imidazoles)</u>		
Butoconazole	C	VC
Clotrimazole	C, L, S, T, VT	D, CC, OC, VC
Econazole	C	D, CC
Ketoconazole	C, S	D, CC
Miconazole	C, L, S, P, VS	D, CC, VC
Oxiconazole	C, L	D, CC
Sulconazole	C, S	D, CC
Terconazole	C, VS	VC
Tioconazole	C, VO	VC

C: cream L: lotion

NL: nail lacquer O: ointment

OS: oral suspension P: powder

S: solution/spray VO: vaginal ointment

VS: vaginal suppository T: troche VT: vaginal tablet

D: dermatophytosis CC: cutaneous candidiasis

OC: oropharyngeal candidiasis VC: vulvovaginal candidiasis

Chemical Class Generic Name	Formulations	Indications
<u>Allylamines</u> and other non-azole ergosterol synthesis inhibitors		
Amorolfine	NL	O
Butenafine HCl	C	D
Naftifine	C, O, P	D
Terbinafine	C, S	D
<u>Other agents</u>		
Ciclopirox olamine	C, L	D, CC
	NL	O
Haloprogin	C	D, CC
Tolnaftate	C, S, P	D
Undecylenate	C, P, O, S	D

C: cream L: lotion

NL: nail lacquer O: ointment

OS: oral suspension P: powder

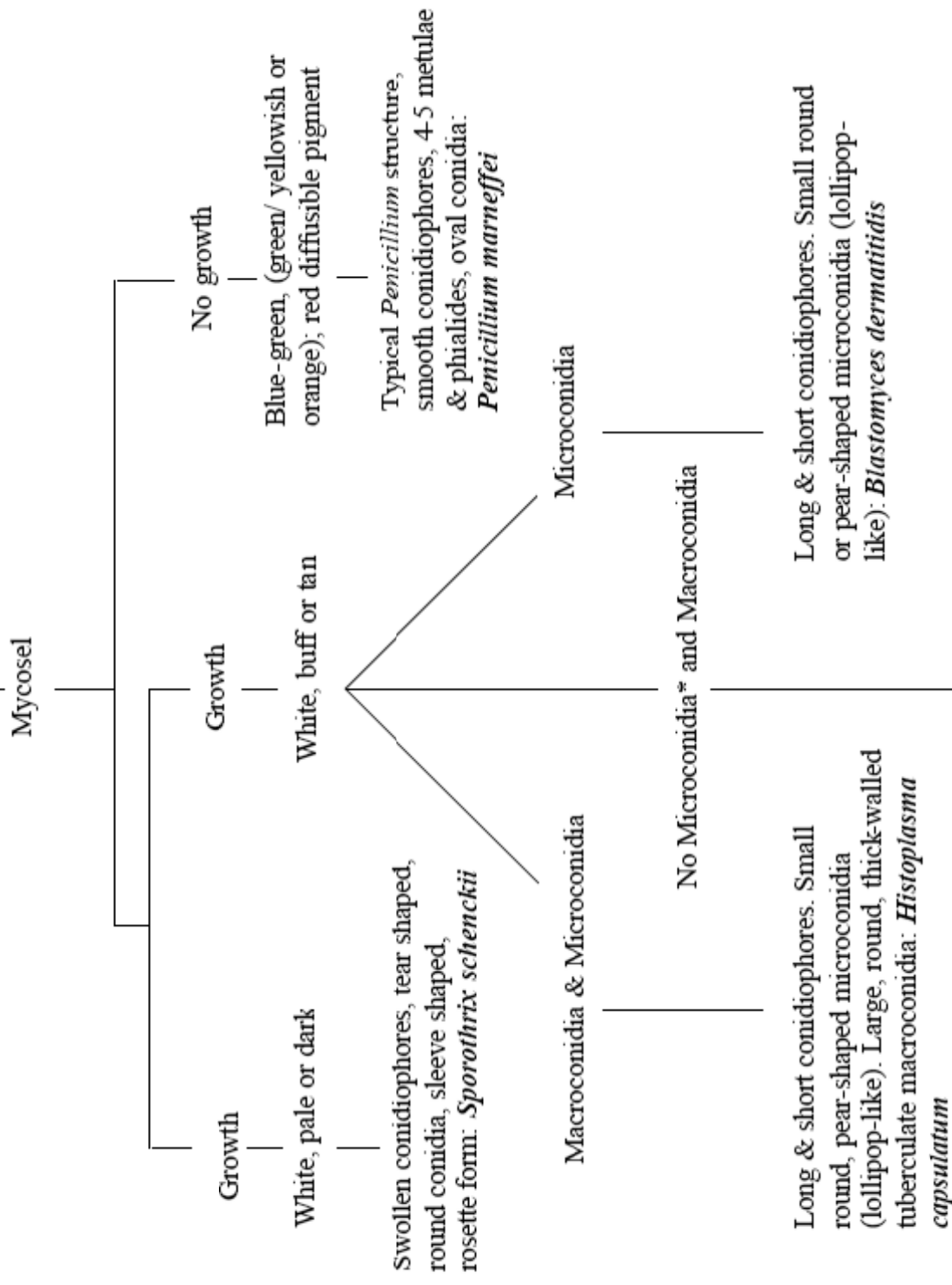
S: solution/spray VO: vaginal ointment

VS: vaginal suppository T: troche VT: vaginal tablet

D: dermatophytosis CC: cutaneous candidiasis

OC: oropharyngeal candidiasis VC: vulvovaginal candidiasis

Dimorphic Fungi (mycelial phase)



Septate hyphae, intercalary and terminal chlamydospores

* Microconidia (rare) along hyphae may be seen:

Paracoccidioides brasiliensis



Definitions and Nomenclature

http://labmed.ucsf.edu/education/residency/fung_morph/fungal_site/page1.01.html#cleistothecia

Anamorph

Asexual or "imperfect" form of a fungus; for example, *Scedosporium apiospermum* is the anamorphic form of the teleomorph *Pseudallescheria boydii*

Arthroconidia

Conidia arising from pre-existing cells in the mycelium; adjacent cells collapse to release the mature form; see, for example, *Geotrichum* and *Coccidioidomycosis*



Ascospore

Sexual spore produced in a sac-like structure called an ascus

Blastoconidia

One of three types of vegetative "spore" arising directly from the vegetative mycelium; budding form, e.g. seen in yeasts

Chlamydoconidia

Conidia arising from pre-existent cells in the hyphae, which thicken and enlarge; may be intercalary, sessile, or terminal

Columella

The swollen, dome-shaped tip of a sporangiophore that extends into the sporangium



Conidia

(singular conidium) Asexual "spores" of fungus

Conidiophore

Specialized hyphal element bearing conidia

Holomorph

Taxonomic name including teleomorphic and anamorphic forms of a fungus; the name of the teleomorph also serves as the name of the holomorph

Hyphae

(singular hypha) The fundamental, threadlike structure of molds

Metula

(plural metulae) Structure below the phialide in some *Penicillium* and *Aspergillus* species; see for example *Aspergillus terreus*



Mycelium

(plural mycelia) The mass of filaments that constitutes the body of a mold; may be vegetative or aerial (reproductive)

Phialide

A conidiogenous cell that produces conidia from within its apex, which does not increase in width or length during conidiogenesis

Rhizoid

Root-like, branched hyphae which usually extend into growth medium; found especially in *Zygomycetes*. See, for example, *Rhizopus*

Sporangia

A fruiting body which forms a closed sac; see, for example, *Absidia*, *Rhizopus*